The Clinical Carbetocin Myocardium Trial

Protocol Identification Number: CarbetocinHeart2014

EudraCT Number: 2014-000507-27

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Participating Departments:

Department of Cardiology, OUH, Department of Cardiology, Vestre Viken Trust, Drammen, Department of Obstetrics and Gynecology, OUH, Department of Clinical Biochemistry, OUH, Department of Clinical Biochemistry, Vestre Viken Trust, Drammen, Department of Biostatistics and Epidemiology, OUH, Department of Clinical Research Support, OUH, Department of Pain Medicine, Division of Emergencies and Critical Care, OUH, Department of Anaesthesiology, Akershus University Hospital.

SPONSOR SIGNATURE PAGE

Title **The Clinical Carbetocin Myocardium Trial – Part II**

Protocol ID no: CarbetocinHeart2014

EudraCT no: **2014-000507-27**

Sponsor signatory approval

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Kristin Sem Thagaard (sponsor)
Head of Department of Emergencies and Critical Care

Kristin Sem Thagaard 03.05.19

Sponsor signature *Date*

PI signatory approval

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Leiv Arne Rosseland,
Professor DMSc MD

LA Rosseland 14.05.19

PI signature *Date*

PROTOCOL SYNOPSIS

The Clinical Carbetocin Myocardium Trial – Part II

Investigational Medicinal Product:	Carbetocin (Pabal®) inj + Oxytocin (Syntocinon®) inj
Centers:	Oslo University Hospital
Study Period:	Estimated date of first patient enrolled in CMT-study part II: 01-01-2019 Anticipated recruitment period: 2 years Estimated date of last patient completed: 31-12-2020
Treatment Duration:	1 minute
Follow-up:	48 h
Endpoints:	Primary endpoint: plasma Troponin I concentrations Secondary endpoint: Other relevant myocardial markers, blood loss, uterine tone, adverse events rate, pain, and ECG changes.
Study Design:	Parallel group, blinded, randomized comparison with oxytocin
Main Inclusion Criteria:	Healthy pregnant women for elective caesarean section age 18 to 50 years
Sample Size:	240 patients
Efficacy Criteria:	Blood loss
Safety Criteria:	Plasma concentration of myocardial biomarkers. Adverse events.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AE	Adverse Event
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electro Cardiography
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug
MV	MetaVision
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SD	Stable Disease
SDV	Source Data Verification
SOP	Standard Operating Procedure
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1 INTRODUCTION

1.1 Background –Treatment

Caesarean delivery is a commonly performed surgical procedure. Uterus contraction after delivery of the baby is necessary to avoid excessive bleeding.

1.2 Background - Therapeutic Information

Adequate uterus contraction after delivery of the baby is necessary to avoid excessive bleeding. Prophylactic administration of an oxytocin receptor agonist is first line practice. Intravenous injection of oxytocin has been the standard procedure but serious cardiovascular adverse events have been reported. Lowering the dose or administering the drug as a 5 minute infusion may increase safety. Carbetocin, a synthetic oxytocin receptor agonist, has significantly longer half life and may reduce blood loss compared with oxytocin. The hemodynamic vasodilatory effects are comparable to oxytocin(1), but potential differences in adverse effects on myocardium are not well described yet.

1.3 Pre-Clinical & Clinical Experience with Carbetocin (IMP) and Oxytocin

Carbetocin has been in clinical use in EU for some years and the efficacy is documented in several RCTs. In the proposed study, carbetocin will be used within the conditions of the marketing authorization. Oxytocin is the first line treatment and prophylaxis in Norway and most countries in the world. According to recently published guidelines from EU drug authorities (EMA), oxytocin should be given as a slow, 5-minute infusion in order to avoid hypotension. This has so far not been implemented in Norway. The pre-clinical and clinical experience of the two drugs are summarized in the Summaries of Product Characteristics.

1.4 Rationale for the Study

Pregnancy and delivery is a natural process, but for many women this period is stressful and not without risks of morbidity, and even mortality. Circulatory adverse events leading to death has been reported after intravenous injection of oxytocin.(2) Some studies indicate that oxytocin may lead to dose dependent ischemic ECG changes(3;4), prolongation of QT time and liberation of biomarkers of myocardial cell death.(3) Previously we have demonstrated comparable vasodilatory effects of oxytocin and carbetocin.(1) There is no clinical study comparing the specific myocardial effects of oxytocin with carbetocin. It may have great impact on the choice of standard medication if the cardiotoxicity of carbetocin is lower compared with oxytocin. The study of potential cardiotoxicity has to be performed in healthy women. Knowing that millions of laboring women have had uneventful injections of oxytocin and carbetocin after delivery, there is probably no reason to fear long lasting negative effects of either drug. If there are differences in cardiotoxicity, this new information should be taken into consideration when planning delivery in pregnant women with heart disease.

2 STUDY OBJECTIVES

The aims of this study are to compare 0h (before C-section) plasma concentrations of Troponin I (high sensitive methods) with a second measurement of plasma concentration of Troponin I drawn within an interval of 6 to 10 hours after administration of study drug, in elective healthy C-section patients randomized to oxytocin 2.5 U or carbetocin 100 µg, 1 minute injection immediately after delivery.

2.1 Primary Endpoint

Primary outcome measure is the difference in plasma concentration of Troponin I from baseline (0h) to the second measurement 6-10 hours after test drug administration, according to treatment allocation. Plasma concentrations will be collected before C-section, and at an interval of 6-10 h after test drug administration.

2.2 Secondary Endpoints

- Other myocardial biomarkers
- Uterus tone evaluated repeatedly
- Blood loss (estimated calculated blood loss)
- Postoperative pain and side effects.
- BP, heart rate and ECG changes

3 STUDY POPULATION

3.1 Selection of Study Population

3.2 Number of Patients

40 patients were included in the pilot trial. In this double blinded randomized controlled trial, elective healthy C-section patients were randomized to oxytocin 2.5 U or carbetocin 100 µg. Plasma level of troponin I was measured at 0h, 4h, 10h and 24h after administration of study drug. The largest difference in plasma troponin I level was found at 10 hours, mean change 0.41 (SD 0.79) in group A versus mean change of 1.78 (SD 4.48) in group B. Statistical power analysis and group size estimation have been performed based on the results from the pilot trial, and we will need to include 178 patients in the confirmatory trial. In the part-2 study, troponin I level will be measured at two time points, at baseline and at an interval of 6-10 hours after administration of study drug. To adjust for missing values and drop outs, 240 patients will be included in the larger confirmatory study, CMT-part 2.
The same protocol that lay the foundation of the pilot trial will serve as protocol for the larger follow up study including 240 patients. Some endpoints will be omitted at selected study sites in this large randomized controlled trial.

3.3 Inclusion Criteria

1. Healthy pregnant women age 18 to 50
2. Singleton pregnancy at gestational age 36 weeks or more
3. Able to read and understand Norwegian.
4. Patients will be recruited from the general population at the birth clinic at Oslo University Hospital or the birth clinic of Akershus University Hospital. Signed informed consent form (ICF) and expected cooperation of the patients for the treatment and follow up will be obtained and documented according to ICH GCP, and national/local regulations.

3.4 Exclusion Criteria

1. Patients with placenta pathology such as praevia, acreta, pre-eclampsia
2. Patients with bleeding disorders including vonWillebrand disease type I.

3. Known intolerance to one of the two drugs.
4. Patients with prolonged QT-time or other serious cardiac diseases.
5. Liver or kidney failure.
6. Epilepsy.
7. Any medical reason why, in the opinion of the investigator, the patient should not participate.

4 Overall STUDY Design

The study is a parallel, randomized, blinded phase 4 study (safety)

Study Period	Estimated date of first patient enrolled in CMT-study part II: 01-01-2019
	Anticipated recruitment period: 2 years
	Estimated date of last patient completed: 31-12-2020
Treatment Duration:	1 minute
Follow-up:	48h

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Dosage and Drug Administration

Carbetocin (Pabal, Ferring Medical, Copenhagen, DK) 100 µg/ml, 1 ml diluted in normal saline to 5 ml will be injected slowly intravenously (1 minute duration). Control intervention is oxytocin (Syntocinon, Swedish Orphan Biovitrum, Stockholm, Sweden) 5 U/ml, 0.5 ml diluted in normal saline to 5 ml will be injected slowly intravenously (1 minute duration).

5.2 Duration of Therapy

The IMPs will be injected slowly (1 minute). The patients will be followed 48h.

5.3 Premedication and Monitoring (if applicable)

Preoperative blood sample will be analyzed for baseline values of interest regarding the study outcome measures, Troponin I, high sensitive methods. There will be no premedication.

5.4 Schedule Modifications

N.a.

5.5 Concomitant Medication

In case of uterus atony, patients will be treated with oxytocin 1 U every 2 minute up to maximum 5 U. Any additional treatment of uterus, medical or surgical, will be decided by the attending obstetrician and anesthesiologist according to departmental procedures. Spinal anesthesia will be given according to departmental procedure, hypotension prophylaxis (phenylephrine 0.1 mg/ml) and intravenous volume (normal saline 10 ml/kg starting concomitantly with spinal anesthesia (see 6.2.2 for details). Pain intensity and opioid consumption will be registered for the patients included at Rikshosptalet, OUH, only. For these patients (Rikshospitalet, OUH) pain treatment protocol includes oral paracetamol 1 g and ibuprofen 400 mg 4 times pr day and IV morphine administered according to departmental procedure using a patient controlled analgesia pump (PCA). All interventions, including all administered medication will be registered with doses and timing.

5.6 Subject Compliance

N.a.

5.7 Drug Storage and Accountability

Drug preparation will be immediately before administration and prepared syringe will be destroyed if not used within 24h after preparation. All IMP use will be accounted for with registration of amount used, date given, batch, expiry date and the trial participant the IMP has been given to. Both oxytocin and carbetocin are in routine use in the department of anesthesiology and are easily accessible for the person responsible for preparation of study drug.

5.8 Drug Labeling

The investigational medicinal product will have a label permanently affixed to the outside and will be labeled according with ICH GCP and local regulations (4.4."Merking av utprøvingspreparatet "in FOR 2009-10-30-1321 Forskrift om klinisk utprøving av legemidler til mennesker and Veiledning til forskrift av 30. oktober 2009 om klinisk utprøving av legemidler til mennesker versjon 2.0./8.-sept-2011.)

- (In Norwegian)

Til klinisk utprøving

CarbetocinHeart2014 Batch nr:_____

Ansvarlig: Dr.Rosseland (Tlf 92204274)

PAS. NR. |__|__| Oslo Universitetssykehus

Til iv injeksjon (60 sek)

Carbetocin 100 µg eller Oxytocin 2,5 IE

Oppbevares i kjøleskap (2°C-8°C),

Holdbar 24 t til kl |__|__|:|__|__|

Dato: ..... Signatur: .....

6 STUDY procedures

6.1 Flow Chart

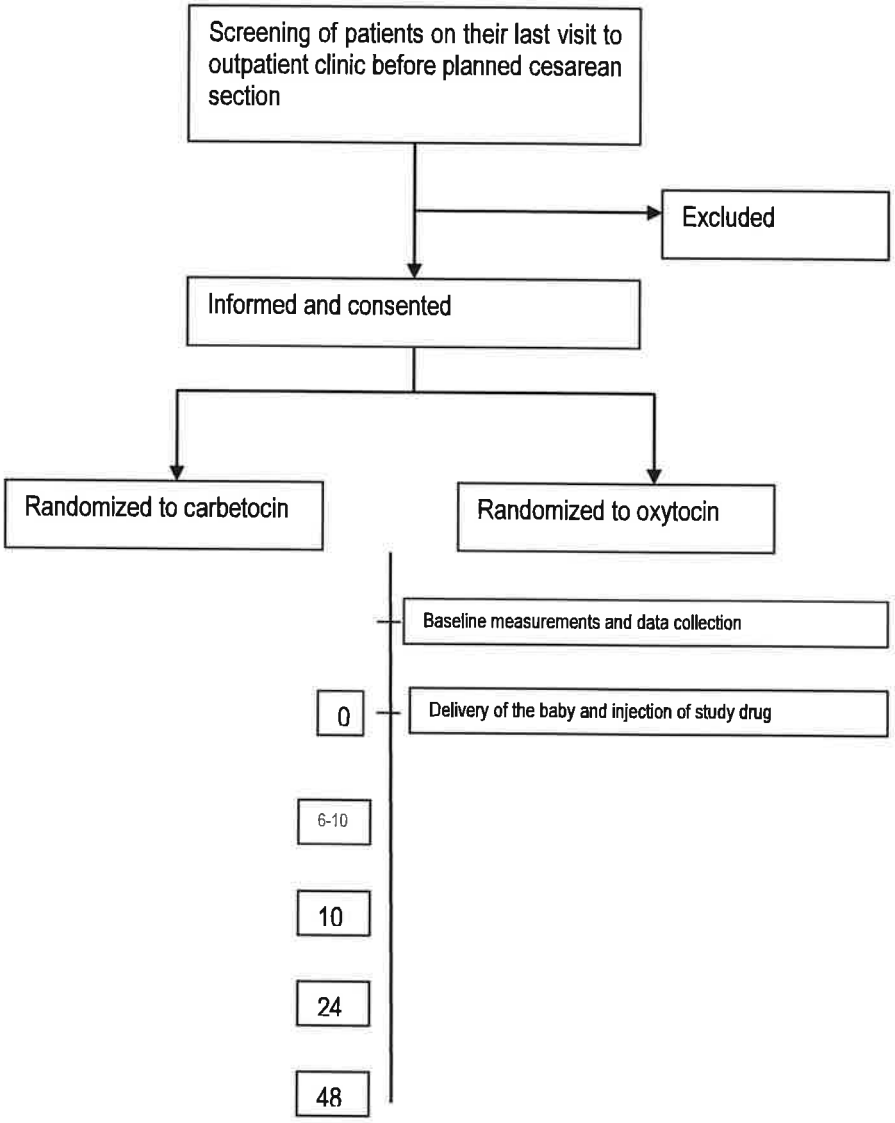

Table 1. Trial flow chart

	Screening Period		Treatment Period	Treatment Period	Treatment Period	Treatment Period			End of study
Time	**Within 14 days of treatment**	**Within 2 h of treatment**	**Time 0 (before C-section)**	**Time after C-section – 0 - 30 min**	**Time 4h**	**Time 6-10h**	**Time 24h**	**Time 48h**	**Time 48h**
Informed consent	X	X							
Inclusion/exclusion Evaluation	X								
Medical History	X								
Demographics[1)]			X						
Vital signs[2)]			X	X					
Blood samples[3)]			X			X			
IMP administration			X						
Uterine tone				2.5 and 5 min					
Adverse event, pain intensity (only for patients at RH,OUH)			X	X	X	X	X	X	X
Record of concomitant medication		X		X					

1. Demographics including pre-pregnant weight, actual weight, height, age, gestational weeks, parity at baseline.
2. Blood pressure, heart rate, ECG, at baseline and until 30 min.
3. Hb, Na, Troponin I.

6.2 By Visit

6.2.1 Before Treatment Starts

Potentially eligible participants will be screened by the principal investigator for inclusion at their last midwife consultation before their scheduled delivery. At Rikshospitalet, OUH, an additional screening of psychological distress and pain catastrophizing will be administered by self-report during the visit in order to assess a potential association with adverse events (post-surgical pain). Oral and written information will be given to each woman at least 24 h before her delivery and written informed consent obtained before randomization. Consent (ICF), participation and redrawal of consent will be documented in electronic patient journal (see 9.2). Name of trial, eligibility, date of signed consent and randomization number will be documented. Screened, but not consented patients will be registered by number. Screened but not included due to exclusion criteria or unfulfillment of inclusion criteria will be registered by number and reason for non-inclusion/exclusion.

6.2.2 During Treatment

Vital signs, preoperative pain status, and baseline blood samples will be registered before anesthesia. Spinal anesthesia will be given according to departmental procedure. During surgery, the patient will be supine with a left lateral tilt (operating table tilt, or operating wedge under her right hip). Hypotension (systolic arterial pressure <90 mmHg) is treated with an extra i.v. bolus of phenylephrine if the heart rate is above 60 beats/min or with i.v. ephedrine 5–10 mg if 60 beats/min or below. The level of anesthesia will be tested by cold sensation 5 min after spinal anesthesia as well as by pinching with surgical tweezers before horizontal skin incision (Pfannenstiel). The study drug will be injected slowly, over the course of 60 s, starting when the baby's head and shoulders is delivered. Exteriorization of the uterus is performed routinely according to departmental policy. The patient will be asked if she experienced any of the listed side effects, and to grade the intensity of the side effects as mild, moderate, or severe. The duration of the side effects will also be recorded. Side effects, pain intensity and medications will be registered until 48h. Registration of side effects will be performed at the following intervals, 0-2 minutes, 2-5 minutes and 5-10 minutes after study drug administration. The rest of the observation period side effects will be registered when reported by the patient.

The obstetrician in charge of the Cesarean delivery assess uterine tone 2.5, and 5 min after administration of study drug, using a numeric rating scale that range from 0 to 10, where a score of 0 means "no effect", 10 means "maximal uterus contraction", and 7 indicates "clinically satisfactory contraction". This uterine contraction scale was introduced to the obstetricians earlier in a previously published RCT. Because visual assessment of blood loss during delivery is of limited value, we will calculate estimated blood loss using the formula for calculated estimated blood loss as published by Stafford(5), revised with weight in kg (last measurement prior to operation), height in cm.(1)

Routine assessments of newborn status are registered (Apgar 1 and 5 minutes, umbilical vein and artery acid-base status).

6.3 Criteria for Patient Discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:

1. Voluntary discontinuation by the patient who is at any time free to discontinue her participation in the study, without prejudice to further treatment.

2. Severe non-compliance to protocol as judged by the Principal Investigator.

3. Incorrect enrolment i.e., the patient does not meet the required inclusion/exclusion criteria for the study.

6.4 Procedures for Discontinuation

6.4.1 Patient Discontinuation

Patients who withdraw or are withdrawn from the study, will stop further treatment.

Patients who withdraw or are withdrawn from the study before randomization, will be replaced.

6.4.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the sponsor (Kristin Sem Thagaard) or PI (Leiv Arne Rosseland) in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration.
- Medical or ethical reasons affecting the continued performance of the trial.
- Difficulties in the recruitment of patients.

The principal investigator will inform the relevant regulatory authorities of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the relevant authorities should be informed within 15 days.

6.5 Laboratory Tests

The aims of this study are to compare baseline plasma concentrations of Troponin I (high sensitive methods) with a second measurement drawn within an interval of 6 to 10 hours after administration of study drug. Blood samples are collected by laboratory personnel who also store the plasma aliquots in the biobank freezer. The project will establish a research biobank at Oslo University Hospital. Some blood tests will be analyzed consecutively at Oslo University Hospital. Some biomarkers of specific scientific interest, such as Troponin I will be analyzed at Vestre Viken Trust, Drammen Hospital when the last patient has been included and after 48h follow up.

7 Efficacy assessments

7.1 Assessment of Efficacy

The primary outcome measure is the difference in change of plasma concentrations of Troponin I from baseline to the second measurement 6-10 hours after test drug administration, according to treatment allocation. Based on the results from the pilot trial (N=40), 240 patients will be included in the larger follow up trial, CMT-part II.

7.2 Biobank

Blood samples will be handled by staff at Department of Clinical Biochemistry, OUH, stored in the specific biobank according to the internal regulations and procedures at OUH.

8 Safety assessments

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to inform the investigator immediately should they manifest any signs or symptoms they perceive as adverse.

The safety data are the outcome measures in the study (cardiovascular biomarkers, continuous monitoring of vital signs, ECG, blood pressure) and the registration of side effects and adverse events during the continuous bedside communication with the patient. Troponin I (high sensitive method) will be analyzed after entering all data on the last patient. Hence, these lab results will not lead to changes in the study. Patients experiencing signs and symptoms of myocardial distress will have a ECG and additional blood tests as clinically indicated follow up.

8.1 Definitions

8.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The term AE is used to include both serious and non-serious AEs.

Expected side effects are defined in 8.2. The participating patients will be informed about the expected side effects prior to inclusion and instructed to score grade of side effects at intervals of 0-2 minutes, 2-5 minutes and 5-10 minutes after injection. It is expected that all adverse events are unlikely after 10 minutes but possible AE occurring after 10 minutes will be registered until end of trial (48h). The patients are asked to grade the degree of side effects as mild, moderate and severe. In case of grades 4 and 5, according to NCI Common Terminology Criteria for Adverse Events, this will be registered by the investigator.

Patient follow up will be completed 48h after injection and this defines the AE period. Unexpected AE/SAE will be reported, also after this period, until discharge from the hospital.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.

- Results in persistent or significant disability or incapacity.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

8.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered;

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Suspected Unexpected Serious Adverse Reaction: Unexpected Adverse Reaction that:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

8.2 Expected Adverse Events

Expected side effects are feeling of warmth, chest pain, shortness of breath, palpitations, flushing, headache, nasal congestion, xerostomia, and metallic taste or other events or reactions listed in the SmPCs of the investigational medicinal products. Both drugs in the study will lead to vasodilatation with decrease in blood pressure and increasing heart rate.

8.3 Time Period and Frequency of Detecting AE and SAE

The standard time period for collecting and recording AE and SAEs will be 0 to 48h after study drug injection for each patient. Unexpected AE/SAE will be reported also after this period until discharge from the hospital.

During the course of the study all AEs and SAEs will be proactively followed up for each patient; events will be followed up to resolution. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

8.4 Recording of Adverse Events

If the patient has experienced adverse event(s), the investigator will record the following information in the CRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).

- The duration of the event will be described in terms of event onset time and event ended data.
- The intensity of the adverse event will be described according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).
- The Causal relationship of the event to the study medication will be assessed as one of the following:

  Unrelated:

  There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

  Unlikely:

  There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.

  Possible:

  There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.

  Probable:

  There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

  Definite:

  There is a reasonable causal relationship between the investigational product and the AE.

  Comment: Dechallange – rechallange of IMPs is not possible in this patient population.

8.5 Reporting Procedure

8.5.1 AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in section 8.1.1 will be recorded in the patient's CRF.

Every SAE will be documented by the investigator on the SAE pages (see CRF page 4). The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter. The principal investigator will inform the sponsor (Kristin Sem Thagaard, Division of Emergencies and Critical Care, Oslo University Hospital) within 24h.

The principal investigator keeps detailed records of all SAEs and performs an evaluation with respect to seriousness, causality and expectedness.

8.5.2 SUSARs

SUSARs will be reported to the Competent Authority. The following procedure will be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions will be reported in an unblinded manner to the Competent Authority concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor. In order to keep the investigator and other persons generating data to the study blinded, the unblinding and the reporting will be performed by Department of Clinical Research Support.

SUSARs will be reported using the CIOMS form since Oslo University Hospital is not connected to EudraVigilance.

8.5.3 Annual Safety Report

Once a year throughout the clinical trial, the sponsor will provide the Competent Authority with an annual safety report. The format will comply with national requirements and follow guidelines published at www.norcrin.no.

8.5.4 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

8.6 Procedures in Case of Emergency

Medical treatment of serious events will be according to international guidelines described in local procedures in Oslo University Hospital (E-håndbok). The PI and the sponsor will decide how to handle each serious patient event. Emergencies will be treated as usual, by the personnel specially trained in relevant medical emergencies.

9 The investigator recording of data and source verification

9.1 Case Report Forms (CRFs)

Electronic Case Report Forms (eCRF) will be provided for the recording of all data. The software Viedoc™ Version4, approved by local data protection office at OUH, serves at as base for the eCRF. Every investigator responsible for entering data into the eCRF will be provided with a unique identity and password, thereby creating an electronic signature of the investigator attesting the accuracy of the data on each eCRF. If any assessments are omitted, the reason for such omissions will be noted on the eCRFs. Corrections, with the reason for the corrections if applicable, can easily be traced by date and signature in the eCRF.

9.2 Source Data

The medical records for each patient should contain information which is important for the patient's safety and continued care and to fulfill the requirement that critical study data should be verifiable. To achieve this, the medical records (MetaVision electronic anesthesia version (MV), or DIPS, or similar of each patient should clearly describe at least:

- That the patient is participating in the study, e.g. by including the enrollment number and the study code (CarbetocinHeart2014)(MV);

- Date when ICF was obtained from the patient and statement that patient received a copy of the signed and dated ICF (DIPS);
- Results of all assessments confirming a patient's eligibility for the study (DIPS);
- Diseases/patient history (past and current; both the disease studied and others, as relevant) (DIPS);
- Treatments given, changes in treatments during the study and the time points for the changes (MV);
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments (MV);
- Date of, and reason for, discontinuation from study treatment (DIPS);
- Date of, and reason for, withdrawal from study (DIPS);
- Additional information according to local regulations and practice (DIPS).
- Some blood analyses will be analyzed consecutively (Hb and Na) and these data will be entered into the database when made available.

  Troponin I analyses will be performed in one batch when all patients are included and the follow up period is over (48h). A biobank consisting of blood samples marked by patient number (not initials or any person identification) will be established. This biobank will consist of aliquots of plasma, stored in a certified biobank freezer (-70 °C), and transported to department of clinical biochemistry, Vestre Viken Trust– Drammen Hospital for final analyses.

- Electronic files, including the data from CRF entered into an electronic database software (Viedoc™ Version4), will be stored at the research server at Oslo University Hospital. This data storage is administered by the Data Inspectorate's local representative who also will handle the application for approval of data storage and ICF.

9.3 Source Data Verification

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check and collect completed CRFs, discuss the progress of the study and monitor drug usage according to ICH GCP. The monitoring will also include source data verification (SDV).

All data will be entered into a computer database at Oslo University Hospital for further handling.

Sponsor's representatives, Department of Clinical Research Support, and Norwegian Medicines Agency will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

9.4 Storage of Study Documentation

The patient identification and the code list will be kept by the PI in a locked office. Patient files will be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc) will be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

10 Statistical considerations

10.1 Determination of Sample Size:

Based on the primary endpoint of interest, Troponin I, group size in order to detect statistically significant differences between the two treatments will be calculated. This is the first clinical study comparing these outcome measures and calculation of statistical power and group size estimations will be calculated from a stage one study/pilot study including 40 patients. Inclusion of patients in the pilot trial was completed in June 2018. In this double blinded randomized controlled pilot trial, elective healthy C-section patients were randomized to oxytocin 2.5 U or carbetocin 100 µg. Plasma level of troponin I was measured at 0h, 4h, 10h and 24h after administration of study drug. The largest difference in plasma troponin I level was found at 10 hours, mean change 0.41 (SD 0.79) in group A versus mean change of 1.78 (SD 4.48) in group B.

Statistical power analysis and group size estimation have been performed by a medical statistician (Morten Wang Fagerland), based on the results from the pilot trial. We will need to include a minimum of 178 patients in the confirmatory trial. In the part-2 study, troponin I level will be measured at two time points, at baseline and at an interval of 6-10 hours after administration of study drug. To adjust for reduced number of troponin I measurements, missing values and drop outs, 240 patients will be included in the larger confirmatory study, CMT-part 2.
The same protocol that lay the foundation of the pilot trial will serve as protocol for the larger follow up study including 240 patients.

10.2 Randomization and blinding

After inclusion patients will be randomized to one of two arms. Randomization list will be made by a researcher not involved in the data collection using randomization software. The randomization responsible will decide block size and if variable block size will be used. Randomization will be initiated at the first registration of the patient in the electronic CRF, however the result of the randomization with regard to the treatment allocation will be unavailable to all the members of the study team with the exception of the person responsible for preparing the syringes and the person generating the randomization list. These persons will not be the same as the one responsible for analysis of the trial data. A detailed procedure for the person responsible for preparing the syringes is stored in the Investigator Site File at the respective study site.

Department of Clinical Research Support will be responsible for sending SUSARs to the Competent Authority and will also have a randomization list available. Unblinding of one or more patients will be performed by this third party only.

In case of need, emergency unblinding of one single patient with regard to treatment allocation may be performed by the personnel responsible for preparation of study drug or by the principal investigator, as described under 8.6.

Blinding of study drug will be secured by using standard 10-ml syringes marked with information as described under 5.8.

10.3 Statistical Analysis

The statistical test will be ANCOVA, probably MIXED MODEL in SPSS, or similar, for repeated measurements with main outcome group differences in the interaction of time and treatment allocation. *Ho hypothesis will be no*

difference between the treatments. Level of statistical significance will be $\alpha<0.05$ and $1-\beta$ 0.8. These principles will be utilized in both stage one of the study and the main study.

Primary efficacy variable is troponin I. Intention to treat analyses will be performed and group differences in side effects will be analyzed and presented regardless of rejection of the H_0 hypothesis or not. All data will be entered and locked in the database, and treatment allocation information will not be revealed until complete dataset are obtained in the main study.

All adverse events, whether spontaneously reported by the patients or observed by the investigator, will be described and categorized both by their nature and severity using the NCI Common Terminology Criteria for Adverse Events, Version 4.03. An attempt to relate the incidence and severity of adverse symptoms to certain patient characteristics will be made.

11 STUDY MANAGEMENT

11.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

11.2 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) will be notified to and approved by the Norwegian Medicines Agency and the Ethics Committee according to EU and national regulations.

11.3 Audit and Inspections

Authorized representatives of a regulatory authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise, the representatives from monitor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

12 Ethical and regulatory requirements

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

12.1 Ethics Committee Approval

The study protocol, including the patient information and ICF to be used, will be approved by the regional ethics committee before enrolment of any patients into the study.

The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

12.2 Other Regulatory Approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study, including local representatives of Data Inspectorate, Norway ("Personvernansvarlig" at Oslo University Hospital) and Norwegian Medicines Agency. Data security will be handled according to the updated EU general data protection regulations (GDPR).

The protocol will also be registered in www.clinicaltrials.gov before inclusion of the first patient.

12.3 Informed Consent

The investigator will give the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she wants. This will not prejudice the patient's subsequent care. Documented informed consent will be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent (ICF).

A copy of the patient ICF will be given to the patients. The signed and dated ICF will be filed in the Investigator Site File binder. A separate note stating that the patient has been provided with oral and written information about the study and has signed the study ICF will be stored in the patient's electronic medical record at the hospital.

The information will be given to potential participants at least 24h prior to registration of consent followed by randomization.

12.4 Subject Identification

The investigator will keep a list of all patients (who have received study treatment or undergone any study specific procedure) including patient numbers, full names and last known addresses.

The patients will be identified in the CRFs by patient number and birth year.

Number of patients screened, informed, and non-consenting patients will also be registered.

13 Trial sponsorship and financing

The study is supported by an unrestricted grant by the manufacturer of carbetocin (Pabal), Ferring Medical, Geneva, Switzerland. Other expenses will be covered by Division of Emergencies and Critical Care at OUH, Akershus University Hospital or the University of Oslo.

14 Publication policy

All personnel who have contributed significantly with the planning and performance of the study and who qualify according to the Vancouver convention may be included in the list of authors.

Collaborators in the project are: Annetine Staff, Department of Obstetrics, OUH, Vegard Dahl, Department of Anesthesiology, Akershus University Hospital, Signe Søvik, Department of Anesthesiology, Akershus University Hospital, Morten Wang Fagerland (Statistical analyses), Division of Biostatistics, OUS, Ole Geir Solberg (Cardiology), Dep. of Cardiology, OUH, Olav Klingenberg (Biomarker analyses), Dep. of Medical Biochemistry, OUH, Lars Aaberge (Cardiology), Dep. of Cardiology, OUH, and Jon Norseth (Biomarker analyses), Dep. of Medical Biochemistry, Vestre Viken Trust, Drammen Hospital, Eldrid Langesæter, Dep. of Anesthesiology, Division of Critical Care, OUH, Silje Reme (pain sub-study), Dep. of Pain Medicine, Division of Critical Care, OUH, and Maria Egeland Bøgh Bekkenes (PhD candidate, patient recruitment, data collection), Dep. of Anesthesiology, Division of Critical Care, OUH.

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